UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA DENTÁRIA

O EFEITO ANTICARIOGÉNICO DO FOSFOPÉPTIDO DE CASEÍNA – FOSFATO DE CÁLCIO AMORFO

Ana Rita Garcia da Silva Reis

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Dissertação orientada pela Prof.ª Doutora Alda Tavares

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"Eles não sabem, nem sonham,

que o sonho comanda a vida,

que sempre que um homem sonha

o mundo pula e avança

como bola colorida

entre as mãos de uma criança."

António Gedeão. In *Movimento Perpétuo*, 1956.

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LISTA DE ABREVIATURAS E SIGLAS

CASP: *Critical Appraisal Skills Programme.*

CDSR: *The Cochrane Database of Systematic Reviews*.

CINAHL: *Cumulative Index to Nursing and Allied Health Literature*.

CPP-ACP: *Casein phosphopeptide-amorphous calcium phosphate.*

CT: Cromatografia.

DARE: *Database of Abstracts of Reviews of Effects.*

EMBASE: *Excerpta Medical Database.*

Glu: Glutamato.

ILF: *Integrated Fluoresncence Loss*.

LILACS: Literatura Latino-Americana e do Caribe em Ciências da Saúde.

MR: Micro-radiografia.

NTRAG: *Programme of North Thames Research Appraisal Group*.

p.p.m.: partes por milhão.

p/v: peso por volume.

P: Fosfato.

pH: Potencial de hidrogénio.

PubMed: *Public Medicine database.*

QLF: *Quantitative Light Induced Fluorescence.*

RCT: *Randomised Controlled Trial.*

Ser: Serina.

TM: *Trade Mark.*

RESUMO

Objetivo: Realizar uma revisão sistemática, baseada na evidência científica existente, sobre o efeito preventivo ou remineralizante da utilização do CPP-ACP incorporado em pasta dentífrica comparativamente à utilização de uma pasta controlo ou placebo.

Métodos: Foi realizada uma pesquisa manual, em revistas relacionadas com a área de odontopediatria e de dentisteria operatória, e eletrónica nas bases de dados Cochrane Plus, CINAHL, EMBASE, OvidSP, PubMed e LILACS. A expressão de pesquisa utilizada incluiu as palavras-chave e operadores booleanos "Tooth Mousse" OR "MI Paste" OR "Recaldent" OR "CPP-ACP", limitada a ensaios clínicos aleatorizados ou *quasi*-aleatorizados em humanos, *in vivo* ou *in situ* e realizada sem restrições de língua. Todas as publicações até 31 de Janeiro de 2012 foram incluídas. A seleção dos estudos foi realizada por dois revisores independentes pelo seu título e resumo, aplicação dos critérios de inclusão e exclusão previamente definidos e avaliação crítica quanto ao seu mérito científico através ficha *Critical Appraisal Skills Programme* (CASP).

Resultados: Nesta revisão sistemática foi obtido um total de 294 artigos, 4 dos quais satisfizeram positivamente os critérios de pesquisa e obtiveram pontuação positiva na ficha CASP. Os ensaios clínicos avaliados apresentaram diversas limitações metodológicas, originando heterogenidade de resultados. Deste modo, apenas foi possível a realização de uma análise qualitativa destes. Embora os ensaios de Bailey e colegas (2009), de Beerens e coloboradores (2010) e de Bröchner e colegas (2010) não verifiquem diferenças estatisticamente significativas entre os grupos, o estudo realizado por Shen e colegas (2011) demonstra que as pastas com CPP-ACP obtiveram um maior nível de remineralização significativo.

Conclusão: Os estudos clínicos avaliados apresentam várias falhas metodológicas que comprometem os resultados. A literatura científica existente não é suficiente para suportar a evidência clínica do efeito anticariogénico do CPP-ACP.

Palavras-chave: Revisão sistemática, CPP-ACP, MI Paste, Tooth Mousse, remineralização dentária, efeito anticariogénico.

ABSTRACT

Objective: To perform a systematic review, based on existing scientific evidence, on the effect of preventive or remineralizing use of CPP-ACP incorporated into toothpaste compared to the use of a placebo or control paste.

Methods: A manual research was carried out in, journals related to the fields of paediatric dentistry and operative dentistry, and an electronic research was performed in the databases Cochrane Plus, CINAHL, EMBASE, OvidSP, PubMed and LILACS. The search expression used included the keywords and boolean operators "Tooth Mousse" OR "MI Paste" OR "Recaldent" OR "CPP-ACP", limited to randomized or *quasi*-randomised controlled trials, in humans, *in vivo* or *in situ* without language restrictions. All publications by January 31, 2012 were included. The selection of studies was performed independently by two reviewers for their title and abstract, application of inclusion criteria and exclusion previously defined and critical appraisal as to their scientific merit by the Critical Appraisal Skills Programme tool (CASP).

Results: A total of 294 articles was obtained, four of which positively fulfill the search criteria and scored positive on the tool CASP. The clinical trials had methodological limitations resulting in heterogeneity of results. Therefore, it was only possible to perform a qualitative analysis of these. Although the tests of Bailey colleagues (2009), Beerens and colleagues (2010) and Brȍchner and colleagues (2010) did not verify significant statistical differences among groups, the study by Shen and colleagues (2011) demonstrated that the pastes with CPP-ACP had a significantly higher level of remineralization.

Conclusion: The evaluated clinical studies present several methodological flaws that compromise the results. The scientific literature is not sufficient to support the clinical evidence of the anticariogenic effect of CPP-ACP.

Keywords: Systematic review, CPP-ACP, MI Paste, Tooth Mousse, dental remineralization, anticariogenic effect.

ANEXOS

Anexo II

Bases de dados incluídas na Biblioteca Cochrane Plus (Biblioteca Cochrane, 2012):

- *The Cochrane Database of Systematic Reviews* - CDSR.
- *The Cochrane Central Register of Controlled Trials* - CENTRAL.
- *The Cochrane Methodology Register* - CMR.
- *Database Of Abstracts Of Reviews Of Effects* - DARE.
- *Health Techonology Assessment Database* - HTA.
- *NHS Economic Evaluation Database* - EED.
- *About the Cochrane Colaboration.*
- Registo de Ensaios Clínicos Ibero-Americanos.
- Agência Iberoamericana de Avaliação de Tecnologias em Saúde.
- Artigos da revista *"Géstion Clínica y Sanitaria"*.
- Artigos da revista *"Evidencia. Actualizácion en la práctica ambulatoria"*.
- Resumos de revisões sistemáticas pela fundação KOVACS.
- Bandolera (tradução da revista "Los Bandoleros" do *National Health Service* britânico).

Anexo II

As 10 perguntas presentes na ficha *Critical Appraisal Skills Programme* (SPH, 2006):

Critical Appraisal Skills Programme (CASP)

making sense of evidence

10 questions to help you make sense of randomised controlled trials

How to use this appraisal tool

Three broad issues need to be considered when appraising the report of a randomised controlled trial:

- **Is the trial valid?**
- **What are the results?**
- **Will the results help locally?**

The 10 questions on the following pages are designed to help you think about these issues systematically.

The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions.

You are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question.

These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

The 10 questions are adapted from Guyatt GH, Sackett DL, and Cook DJ, Users' guides to the medical literature. II. How to use an article about therapy or prevention. JAMA 1993; 270 (21): 2598-2601 and JAMA 1994; 271(1): 59-63

Screening Questions

1. Did the study ask a clearly-focused question? □ Yes □ Can't tell □ No

Consider if the question is 'focused' in terms of:

– the population studied

– the intervention given

– the outcomes considered

2. Was this a randomised controlled trial (RCT) and was it appropriately so? □ Yes □ Can't tell □ No

Consider:

– why this study was carried out as an RCT

– if this was the right research approach for the question being asked

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Is it worth continuing?

Detailed Questions

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3. Were participants appropriately allocated to intervention and control groups? □ Yes □ Can't tell □ No

Consider:

– how participants were allocated to intervention and control groups. Was the process truly random?
– whether the method of allocation was described. Was a method used to balance the randomization, e.g. stratification?
– how the randomization schedule was generated and how a participant was allocated to a study group
– if the groups were well balanced. Are any differences between the groups at entry to the trial reported?
– if there were differences reported that might have explained any outcome(s) (confounding)

4. Were participants, staff and study personnel 'blind' to participants' study group? □ Yes □ Can't tell □ No

Consider:

– the fact that blinding is not always possible

– if every effort was made to achieve blinding

– if you think it matters in this study

– the fact that we are looking for 'observer bias'

5. Were all of the participants who entered the trial accounted for at its conclusion? □ Yes □ Can't tell □ No

Consider:

– if any intervention-group participants got a control-group option or vice versa
– if all participants were followed up in each study group (was there loss-to-follow-up?)
– if all the participants' outcomes were analysed by the groups to which they were originally allocated (intention-to-treat analysis)
– what additional information would you liked to have seen to make you feel better about this

6. Were the participants in all groups followed up and data collected in the same way? □ Yes □ Can't tell □ No

Consider:

– if, for example, they were reviewed at the same time intervals and if they received the same amount of attention from researchers and health workers. Any differences may introduce performance bias.

7. Did the study have enough participants to minimise the play of chance? □ Yes □ Can't tell □ No

Consider:

– if there is a power calculation. This will estimate how many participants are needed to be reasonably sure of finding something important (if it really exists and for a given level of uncertainty about the final result).

8. How are the results presented and what is the main result?

Consider:

– if, for example, the results are presented as a proportion of people experiencing an outcome, such as risks, or as a measurement, such as mean or media differences, or as survival curves and hazards
– how large this size of result is and how meaningful it is
– how you would sum up the bottom-line result of the trial in one sentence

9. How precise are these results?

Consider:

– if the result is precise enough to make a decision
– if a confidence interval were reported. Would your decision about whether or not to use this intervention be the same at the upper confidence limit as at the lower confidence limit?
– if a p-value is reported where confidence intervals are unavailable

10. Were all important outcomes considered so the results can be applied? □ Yes □ Can't tell □ No

Consider whether:

– the people included in the trail could be different from your population in ways that would produce different results
– your local setting differs much from that of the trial
– you can provide the same treatment in your setting

Consider outcomes from the point of view of the:

– individual

– policy maker and professionals

– family/carers

– wider community

Consider whether:

– any benefit reported outweighs any harm and/or cost. If this information is not reported can it be filled in from elsewhere?

– policy or practice should change as a result of the evidence contained in this trial